

Medical Progress

Managing Malignant Pericardial Effusion

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The involvement of the pericardium by metastatic tumors is not uncommon, particularly in patients with lung cancer, breast cancer, lymphomas, leukemias, and melanomas. There are five therapeutic modalities for the treatment of malignant pericardial effusion, including pericardiocentesis, pericardial sclerosis, systemic chemotherapy, radiotherapy, and surgical treatment. The optimal treatment selection is dependent principally on a patient's life expectancy; responsiveness of the tumor to chemotherapy, irradiation, or both; and whether or not cardiac tamponade is present at diagnosis. The overall prognosis of patients with malignant pericardial effusion is primarily influenced by the extent and histologic features of the underlying cancer. Although this condition is usually incurable, a reasonable period of useful palliation can be obtained in most patients.

(Buzaid AC, Garewal HS, Greenberg BR: Managing malignant pericardial effusion. West J Med 1989 Feb; 150:174-179)

The development of a malignant pericardial effusion in patients with disseminated malignancy is not uncommon. The incidence ranges from 5% to 53% in autopsy and clinical studies and varies with the histologic diagnosis.¹⁻⁸ Because most patients are asymptomatic, the incidence is much higher in autopsy series.⁸⁻¹⁰ The most common tumors to involve the pericardium are lung, breast, lymphomas, leukemias, and melanoma. They account for approximately 75% of malignant pericardial effusions that are clinically diagnosed.¹⁰⁻¹⁶ Nevertheless, any tumor can potentially involve the pericardium and result in an effusion.¹⁷

Malignant pericardial effusion often has an insidious clinical onset that can mimic the picture of disseminated carcinomatosis. Occasionally pericardial involvement may be the first clinical manifestation of an undiagnosed malignant tumor.¹⁸⁻²³ Recognizing its presence is particularly important because of the life-threatening potential of cardiac tamponade. Furthermore, in a review of 55 patients with cancer who had pericardial disease, Thurber and co-workers found that pericardial involvement resulted in or contributed significantly to the cause of death in 85% of patients.⁹ Thus, therapeutic interventions directed at controlling this complication of malignancy can, if successful, result in prolonging survival. The overall survival and quality of life of patients with malignant pericardial effusion is dictated primarily by the histologic type and extent of the underlying malignant process. For instance, in three recent large series where patients were treated surgically or with pericardial sclerosis, those with non-small-cell lung cancer had a median survival of approximately three to four months, whereas those with breast cancer had a median survival exceeding nine months.²⁴⁻²⁶

Because about 40% of patients with a symptomatic pericardial effusion and an underlying cancer may have nonmalignant pericardial disease,²⁷ determining the specific cause is of critical importance.²⁸ In this respect, special attention should be given to those patients who have received prior

irradiation to the precordium because the treatment and prognosis of radiation-induced pericarditis are notably different.²⁹⁻³³ The differential diagnosis should also include idiopathic pericarditis,³⁴ drug-induced pericarditis,³⁵ infection,³⁶ hypothyroidism,³⁷ and autoimmune disorders.^{37,38} In this report we will not discuss the approach to establishing a specific diagnosis but will focus on the management of patients with a known diagnosis of malignant effusion and outline a treatment plan.

Because criteria for response vary among series, a direct comparison of the results of each therapeutic modality is not possible. In the few larger series, however, the criteria outlined by Smith and associates were usually used.³⁹ These are as follows: a decrease or disappearance of pericardial effusion lasting 30 days or more assessed by radiography and clinical examination; an absence of symptoms of pericardial tamponade for more than 30 days; and no requirement for pericardiocentesis 30 days after the initiation of local or systemic treatment. In more recent reports, echocardiography has been included to augment the accuracy of evaluating response.

Currently there are five major methods of treating malignant pericardial effusion: pericardiocentesis, pericardial sclerosis, systemic chemotherapy, radiotherapy, and surgical treatment. The overall treatment plan depends on several factors such as the presence of hemodynamic compromise, the general medical condition of a patient, expertise available at a particular institution, and the extent and histologic features of the tumor. The last clearly has a major effect on the prognosis.

Pericardiocentesis

The major indications for pericardiocentesis are to relieve an impending cardiac tamponade and to palliate symptoms. It also provides important information in patients without a confirmed diagnosis. For this purpose, pericardial fluid should be sent for blood cell and differential counts,

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Supported in part by Cancer Center Core Support Grant No. CA-23074. Dr Garewal is a recipient of an American Cancer Society Career Development Award.

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TABLE 1.—*Intrapericardial Tetracycline Sclerosis in the Treatment of Malignant Pericardial Effusion*

Source	No. of Patients Improved/Total (%)	Mean No. of Instillations Required	Recurrence	Median Survival, days	Side Effects
Davis et al, 1984 ²⁵	30/33 (90)	2.8 (range 1-7)	0	106 (range 28-704)	Fever in 12 patients; 1 episode of atrial fibrillation
Shepherd et al, 1985, ⁵⁹ 1987 ⁶⁰ . .	43/58 (74)	2.9 (range 1-5)	3 (5%)	168 (range 30-1,149+)	Fever in 5 patients; pain in 9; transient atrial arrhythmia in 5; 1 patient had cardiac arrest before tetracycline instillation

TABLE 2.—*Technique for Tetracycline Sclerosis of Malignant Pericardial Effusion*

Do echocardiographically guided pericardiocentesis with an 18-gauge catheter using a standard subxiphoid approach*

Connect the catheter to a Hemovac suction system to drain for 12 to 24 hours

Repeat echocardiography to check if the pericardial sac is "dry" (optional)

Instill 5 ml of 2% lidocaine hydrochloride mixed in 10 ml of normal saline solution 20 minutes before tetracycline instillation

Preadminister medication—50 to 75 mg meperidine hydrochloride intravenously or equivalent narcotic—before sclerosis procedure

Instill 500 to 1,000 mg of tetracycline mixed in 20 ml of normal saline solution into the pericardial sac

Clamp the catheter for 2 hours following tetracycline instillation, then allow it to drain to the Hemovac system

Repeat the procedure every 24 to 48 hours until the net pericardial drainage is 25 ml or less in 24 hours

Repeat echocardiography before removing the catheter to exclude loculation

*This is best done in a critical care area with the availability of electrocardiographic monitoring and resuscitative equipment.

lactic dehydrogenase, total protein, and glucose values, and cytologic study.⁴⁰⁻⁴² Although the results of cytologic study are abnormal in about 80% of cases, an additional test that appears to be useful is measuring the carcinoembryonic antigen levels in the pericardial fluid.⁴³

The standard methods of pericardiocentesis use a subcostal blind puncture or an electrocardiographically guided procedure. Although these techniques may be appropriate in patients with life-threatening cardiac tamponade, they are associated with significant morbidity and mortality, including arrhythmias; damage and perforation of the myocardium; damage to the coronary, pericardial, or internal mammary arteries, leading to hemopericardium, hemothorax, and arteriovenous fistulas; pneumothorax; and, more rarely, damage to the liver with leakage of blood or bile.^{34,44-47}

Recently Callahan and associates described the use of two-dimensional (2-D) echocardiographically directed pericardiocentesis.^{48,49} They reported 132 consecutive procedures carried out in 117 patients. Complications were usually minor and never fatal. In one patient who previously had a right pneumonectomy for lung cancer, a symptomatic pneumothorax developed during the infiltration of a local anesthetic, while another had vasovagal syncope during needle insertion and refused to continue the procedure. In two patients, the right ventricular cavity was entered with a small sheathed needle (16 gauge), but the procedure was completed in both without complications.⁴⁹ Similar results have been obtained by Clarke and Cosgrove using real-time, echocardiographically guided pericardiocentesis.⁵⁰ In contrast to these data, complication rates of pericardiocentesis using either the blind or electrocardiographically guided techniques have been in the range of 7% to 15%,⁴⁴⁻⁴⁷ with a mean mortality rate of 6% (range 0% to 19%) in five large

series.^{34,44-47} Furthermore, the 2-D echocardiographically guided pericardiocentesis can be used in patients who cannot assume a supine position because of dyspnea. In this group of patients, the pericardiocentesis can be done with the patient sitting upright. Another advantage of echocardiographic guidance is that it may occasionally show tumor masses infiltrating the myocardium or protruding from the pericardium or the epicardium into the echo-free space of the pericardial effusion, thus further supporting its malignant origin.⁵¹⁻⁵⁴ For these reasons, whenever possible, it should be the procedure of choice for pericardiocentesis.

Although pericardiocentesis alone can produce prolonged palliation in some patients,^{55,56} additional therapy is usually necessary to ensure adequate control in most patients, particularly in those with a relatively long life expectancy.

Pericardial Sclerosis

Despite the wide acceptance and considerable experience with sclerosing agents in the treatment of malignant pleural effusion,⁵⁷ their use in patients with malignant pericardial effusion is much more limited.

The largest published experience has been with tetracycline, originally reported by Davis and co-workers.⁵⁸ Both their series²⁵ and the University of Toronto's recent update^{59,60} are summarized in Table 1. The most important steps of this technique are described in Table 2. The overall results of both series were similar, with high efficacy and rare recurrences. Three instillations of tetracycline were usually required for optimal results. Although the reported complications were generally minor, in the Toronto series one patient had a cardiac arrest before the tetracycline instillation. To prevent major complications, the insertion of the pericardial catheter should always be done in an intensive care unit. The patient can then be transferred to a general medical ward, but special attention should be directed at accurately recording the pericardial drainage, analgesia, and monitoring of possible cardiac arrhythmias. The mechanism of action of tetracycline is still not completely understood. Analogous to the situation with malignant pleural effusions, it has been speculated that tetracycline can destroy mesothelial cells because of its high acidity (pH 2.0 to 3.0) leading to an inflammatory process and consequent pericardiodesis.^{61,62}

Many other agents have been used for pericardial sclerosis including mechlorethamine hydrochloride, 5-fluorouracil, bleomycin sulfate, thiopeta, quinacrine hydrochloride, talc, and radioactive gold.^{56,63-68} It is difficult to assess their efficacy because their use has been described principally in case reports.

Although the best indications for intrapericardial tetracycline sclerosis are not clearly defined, its application has increased significantly in the past few years, especially in institutions where the availability or experience with the sur-

gical management of malignant pericardial effusion is more limited. Regardless, we strongly favor the use of pericardial sclerosis in the following cases:

- Patients who present with cardiac tamponade or a substantial symptomatic pericardial effusion who require urgent pericardiocentesis to relieve an impending tamponade. In these patients, the catheter used for pericardiocentesis should be left in place for subsequent pericardial sclerosis.
- Patients who do not have either chemotherapy- or radiotherapy-sensitive tumors, especially those who are poor surgical candidates.

Systemic Chemotherapy

Although data concerning the role of systemic chemotherapy in the treatment of malignant pericardial effusion are limited, they do suggest that cytotoxic therapy may be effective in chemotherapy-sensitive tumors such as lymphomas, leukemias,^{8,69-71} and occasional solid tumors.^{72,73}

Acquatella and colleagues used echocardiography to prospectively evaluate 32 patients with non-Hodgkin's lymphoma⁸ and showed that 17 (53%) had pericardial effusions. Of these, four patients with lymphoblastic lymphoma and extensive mediastinal involvement had clinical and echocardiographic signs of cardiac tamponade. Most patients were treated with CHOP—cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone—or modified-CHOP chemotherapy. The four patients with cardiac tamponade had an initial pericardiocentesis and, in addition to the chemotherapy, received palliative irradiation to the mediastinum. Of the 17 patients, 12 (70%) had complete disappearance of the pericardial effusion, including the 4 patients with cardiac tamponade. Although the follow-up period was short, the presence of a pericardial effusion had no effect on overall survival rates (70% with and 68% without pericardial effusion alive at one year).

Reynolds and Byrne⁷³ reported on three patients with malignant pericardial effusion due to breast cancer in whom control of the effusion was achieved with a single pericardiocentesis followed by intensive systemic chemotherapy. No patient required reaspiration or any other form of local treatment.

Recently Mufti and associates reported the efficacy of antileukemic therapy in four patients with malignant serous effusions due to acute monocytic leukemia.⁶⁹ Of these, one patient had pericardial effusion and had pronounced improvement with systemic chemotherapy alone.

Despite the paucity of published reports regarding the use of systemic chemotherapy in managing malignant pericardial

effusion, the limited information available supports its use in previously untreated patients with highly chemotherapy-sensitive tumors. It can be used alone if there is no evidence of tamponade or combined with pericardiocentesis if tamponade is present.

Radiotherapy

The use of cardiac irradiation alone in the management of malignant pericardial effusion has received little attention in the literature. There are two published series of external irradiation, and their results are shown in Table 3.^{74,75} As expected, radiotherapy was particularly effective in tumors known to be radiosensitive such as Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic leukemia, and breast cancer.^{70,71,74-77}

A different form of radiotherapy was reported by Martini and co-workers from the Memorial Sloan-Kettering Cancer Center (New York)⁷⁸: 28 patients with malignant pericardial effusion were treated by the intrapericardial instillation of radioactive chromic phosphate (³²P). Of these, 20 had no further problems with pericardial effusions after the initial tap and ³²P instillation. Eight required one additional pericardiocentesis one to five months later. Despite its apparent efficacy, this technique has been practically abandoned because of difficulty in handling the radioactive material, the expense, and the availability of other techniques capable of producing similar results.⁶⁶

Radiotherapy is often recommended for patients with radiosensitive tumors such as lymphomas and leukemias.^{39,66} However, because these tumors are also responsive to initial chemotherapy^{8,69-71} and the malignant pericardial effusion usually represents a manifestation of widely metastatic disease, chemotherapy should precede radiotherapy if feasible. We recommend cardiac irradiation primarily in two clinical situations:

- Patients refractory to chemotherapy and who have radiosensitive tumors—such as lymphomas, leukemias, small-cell lung cancer, testicular cancer.
- Patients for whom sclerosis or a pericardial window fails and who are poor candidates for a second invasive procedure—that is, a second pericardial window or pericardial sclerosis—especially those with radiosensitive tumors.

Surgical Treatment

In the past five years, the surgical treatment of malignant pericardial effusion has become more popular, with more than 200 cases having been reported.^{24,79-90} The results of recent surgical series are summarized in Table 4. Most pa-

TABLE 3.—Treatment of Malignant Pericardial Effusions With Radiotherapy Alone

Source	Histologic Diagnosis	No. of Patients Improved/Total (%)	Duration of Improvement, mo
Terry and Kligerman, 1970 ⁷⁴	Hodgkin's disease	4/4 (100)	2,* 9, 12, and 25
	Lymphoblastic lymphoma	1/1 (100)	10*
	Chronic myeloid leukemia	1/1 (100)	10*
	Lymphosarcoma	1/1 (100)	1*
Cham et al, 1975 ⁷⁵	Breast carcinoma	11/16 (69)	2-36 (median 4)
	Lung cancer†	2/7 (28)	1 and 9
	Lymphoma and leukemia	6/7 (86)	2-4
	Miscellaneous	4/8 (50)	1-4

*All patients died without evidence of recurrence of the pericardial effusion.

†Histologic subtype not specified.

tients underwent a pericardial window, usually done with the patient under general anesthesia. In general, surgical treatment was effective and recurrences were rare. Early deaths after the operation (within 30 days) were usually due to the underlying cancer and were not uncommon. This emphasizes the importance of suitable patient selection with special attention to the prognosis of the underlying malignant tumor.

The surgical treatment of malignant pericardial effusion may be accomplished with a subxiphoid approach, a left anterior thoracotomy, or a median sternotomy. Although treatment selection is strongly influenced by the experience with each procedure at a particular institution,⁷⁹ the subxiphoid approach should probably be the procedure of choice because, compared with the other surgical modalities, it is at least as effective and can be done using local anesthesia with overall lower morbidity and mortality.^{82,91} On the other hand, a left anterior thoracotomy, which is still the predominant approach in certain institutions, has the advantage of allowing better exposure of the pericardium and can yield a larger amount of material for diagnostic studies. Nevertheless, it should be reserved for patients who are good surgical candidates because it requires general anesthesia and is associated with higher morbidity.⁷⁹ In this setting, to prevent hypotension from the induction of anesthesia, it is recommended that these patients undergo pericardiocentesis before the operation.

Technically, the subxiphoid pericardial window is a relatively simple procedure that can even be done with the patient in a semisitting position in patients who cannot lie supine because of dyspnea. The major steps involved in this technique are shown in Figure 1. Relative contraindications for a subxiphoid approach, particularly if using local anesthesia, include extreme obesity, a narrow costal angle, and a previous midline abdominal operation.⁸⁶

Patients with constrictive pericarditis represent a distinct group. Constrictive pericarditis may be due to extensive tumorous thickening of the pericardium or irradiation to the precordium. In both cases, an extensive pericardial resection through a median sternotomy is probably the best approach in view of the high incidence of late constrictive pericarditis

in cases managed with a simple pericardial window.^{24,80} Because extensive pericardial resection is associated with significant morbidity and mortality, however, it should be indicated with caution in patients with a poor prognosis and active malignancy and reserved principally for those with radiation-induced constrictive pericarditis who are probably cured of their cancer.⁷⁹

The following are the major indications for surgical intervention:

- Patients with malignant pericardial effusion and anticipated long survival, particularly those for whom irradiation, pericardial sclerosis, or both, have failed.

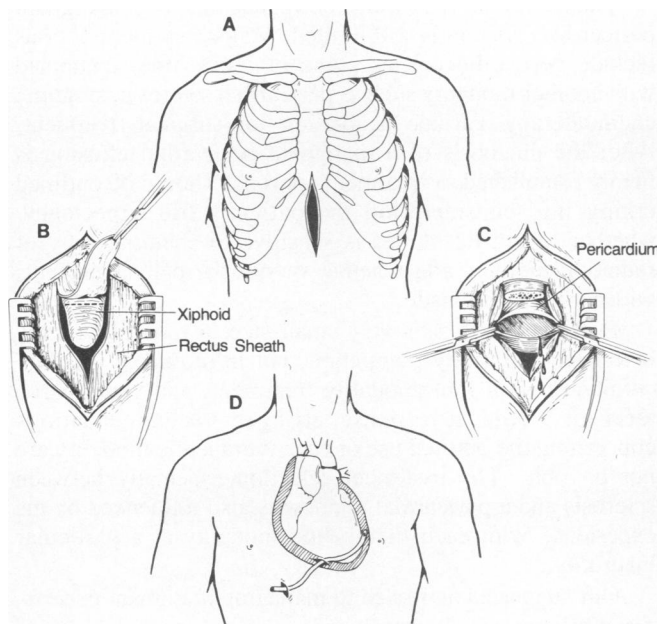


Figure 1.—The subxiphoid technique for creating a pericardial window is shown. **A**, A midline incision is done. **B**, The xiphoid process is removed to provide maximal access to the substernal space. **C**, The pericardium is grasped with clamps and a window is created. **D**, A thoracic catheter is inserted along the inferior aspect of the pericardium.

TABLE 4.—Surgical Treatment of Malignant Pericardial Effusion

Source	No. of Patients Improved/Total (%)	No. of Recurrences (%)	No. of Patients Who Succumbed to Cancer Within 30 Days After Operation (%)	Comments
Piehler et al, 1985 ²⁴	70/72 (97)	3 (4)*	14 (20)	3 recurred at 2.5, 3, and 3.5 months; 23% alive at 1 year
McKenna et al, 1985 ⁷⁹	44/49 (90)	3 (7)	7 (14)	44 underwent pleuropericardial window
Miller et al, 1982 ⁸⁰	26/26 (100)	0	3 (11)	3 who died early all had lung cancer; 19 had breast cancer with 15 alive > 1 year
Gregory et al, 1985 ⁸¹	18/25 (72)	3 (17)	At least 3 (16)	3 recurred at 4, 5, and 6 months
Ghosh et al, 1985 ⁸²	20/20 (100)	Not stated	Not stated	Some patients had the procedure under local anesthesia
Hankins et al, 1980 ⁸³	17/17 (100)	0	6 (35)	2 alive at 8 and 21 months
Osuch et al, 1985 ⁸⁴	12/12 (100)	0	Not stated	Average survival was 6.7 months
Little et al, 1984 ⁸⁵	6/6 (100)	0	4 (67)	All received irradiation to the pericardium after the procedure; 2 alive at 9 and 11 months
Prager et al, 1982 ⁸⁶	5/6 (83)	0	Not stated	5 deaths occurred within 43 days after operation
Alcan et al, 1982 ⁸⁷	5/5 (100)	0	Not stated	2 patients died in hospital; 3 patients also had tetracycline sclerosis
Hill and Cohen, 1970 ⁸⁸	3/4 (75)	1 (33)	0	1 recurred at 13 months; 2 patients received irradiation to the pericardium after the operation
Berman et al, 1984 ⁸⁹	3/3 (100)	0	0	Procedure done using local anesthesia
Liepmann and Goodlerner, 1981 ⁹⁰	2/2 (100)	0	0	Both patients had acute leukemia

*Two cases that recurred within 4 weeks were considered primary failures and not recurrences in this analysis.

- Patients with an underlying malignant tumor and a pericardial effusion who may have benign pericardial disease, such as radiation-induced pericarditis.
- Patients with pericardial effusion, probably malignant in nature, who lack adequate histologic confirmation of malignancy, and a tissue diagnosis is otherwise difficult to obtain.
- Selected patients with a long life expectancy and constrictive pericarditis due to tumorous involvement of the pericardium and patients with radiation-induced constrictive pericarditis.

Conclusions

The literature regarding the management of malignant pericardial effusion is still limited. Major treatment options include pericardiocentesis alone or more often combined with another modality such as pericardial sclerosis, systemic chemotherapy, cardiac irradiation, or surgical treatment. After the diagnosis of a malignant pericardial effusion is firmly established, a treatment approach should be outlined taking into consideration the patient's life expectancy, whether or not the tumor is sensitive to chemotherapy or radiation therapy, and whether or not the patient presents with cardiac tamponade.

Because of the relatively small size of most series, the heterogeneous study population, not infrequently the concomitant use of multimodality treatment, and varying criteria for a clinical response, stringent recommendations concerning the optimal use of each therapeutic modality are not possible. The treatment selection especially between sclerosis and a pericardial window is also influenced by the experience with each therapeutic modality at a particular institution.

Our suggested approach to managing malignant pericardial effusion is as follows:

- Patients with a symptomatic, malignant pericardial effusion, a long life expectancy (more than three months), without cardiac tamponade, whose tumor is not very sensitive to chemotherapy or radiotherapy, such as non-small-cell lung cancer, and who are good surgical candidates may be considered for an elective subxiphoid pericardial window. We would emphasize that this recommendation is dependent on the availability and experience with this surgical approach at each institution. A suitable alternative would be pericardial sclerosis, which, in fact, is the preferred approach in many institutions regardless of the surgical condition of the patient. If cardiac tamponade or significant symptoms are present at diagnosis, pericardiocentesis with subsequent sclerosis using the same catheter is the best initial approach. Pericardial sclerosis should also be considered for those who are poor surgical candidates, such as patients with severe chronic obstructive pulmonary disease.
- Patients with malignant pericardial effusion, no prior chemotherapy, and who have chemotherapy-sensitive tumors (lymphomas, leukemias, small-cell lung cancer, or testicular cancer) should receive systemic chemotherapy. If significant symptoms or cardiac tamponade is present, a pericardiocentesis to relieve symptoms should precede the chemotherapy. Radiotherapy should be considered if chemotherapy fails to control the effusion.
- Patients with malignant pericardial effusion and a short life expectancy (a month or less) should probably undergo

only pericardiocentesis. If frequent pericardiocenteses become necessary, sclerosis should be considered.

- Patients with a history of malignancy who may have benign pericardial disease that cannot be diagnosed by other means, or those with a probable malignant pericardial effusion but who lack histologic confirmation of the type of malignancy and there is difficulty in obtaining a tissue diagnosis from other sites should undergo an operation for diagnosis and treatment.

In choosing a therapeutic plan, it must be remembered that the overall prognosis of patients with malignant pericardial effusion is primarily dictated by the histologic type and extent of the underlying cancer. Except for a few malignant diseases such as lymphomas and leukemias, involvement of the pericardium virtually always reflects incurability. Nevertheless, a nihilistic attitude towards the management of malignant pericardial effusion is not justified because for many patients a reasonable period of meaningful palliation can be obtained.

REFERENCES

1. Javier BV, Yount WJ, Hall TC, et al: The clinical implications of cardiac metastasis from solid tumors—A clinical analysis of 292 cases proved at autopsy. *Neoplasma* 1967; 14:561-574
2. Kline IK: Cardiac lymphatic involvement by metastatic tumor. *Cancer* 1972; 29:799-808
3. Roberts WC, Glancy DL, DeVita VT: Heart in malignant lymphoma (Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and mycosis fungoides): A study of 196 autopsy cases. *Am J Cardiol* 1968; 22:85-107
4. Rosenberg SA, Diamond H, Jaslowitz B, et al: Lymphosarcoma: A review of 1269 cases. *Medicine (Baltimore)* 1961; 40:31-84
5. Markiewicz W, Glatstein E, London EJ, et al: Echocardiographic detection of pericardial effusion and pericardial thickening in malignant lymphoma. *Radiology* 1977; 123:161-164
6. Glancy DL, Roberts WC: The heart in malignant melanoma: A study of 70 autopsy cases. *Am J Cardiol* 1968; 21:555-571
7. Lokich JJ: The management of malignant pericardial effusions. *JAMA* 1973; 224:1401-1404
8. Acquatella GC, Roura ET, Maury AJ, et al: High incidence of pericardial effusion in non-Hodgkin's lymphoma: Usefulness of echocardiography. *Eur J Cancer Clin Oncol* 1982; 18:1131-1136
9. Thurber DL, Edwards JE, Achur RWP: Secondary malignant tumors of the pericardium. *Circulation* 1962; 26:228-241
10. Adenle AD, Edwards JE: Clinical and pathologic features of metastatic neoplasms of the pericardium. *Chest* 1982; 81:166-169
11. Scott RW, Garvin CF: Tumors of the heart and pericardium. *Am Heart J* 1939; 17:431-436
12. Cohen GU, Peery TM, Evans JM: Neoplastic invasion of the heart and pericardium. *Ann Intern Med* 1955; 42:1238-1245
13. Lamberta F, Nareff MJ, Schwab J: Metastatic carcinoma of the pericardium. *Dis Chest* 1951; 19:528-536
14. Prichard RW: Tumors of the heart: Review of the subject and report of 150 cases. *Arch Pathol* 1951; 51:98-128
15. DeLoach JF, Haynes JW: Secondary tumors of heart and pericardium. *Arch Intern Med* 1953; 91:224-249
16. Harrer WV, Lewis PL: Metastatic tumors involving the heart and pericardium. *Pa Med* 1981; 74:57-60
17. Lund B: Pericardial effusion in advanced ovarian carcinoma—A literature review and report of two cases. *Acta Obstet Gynecol Scand* 1985; 64 (suppl):443-445
18. Sulkes A, Weshler Z, Kopolovic Y: Pericardial effusion as first evidence of malignancy in bronchogenic carcinoma. *J Surg Oncol* 1982; 20:71-74
19. Appelqvist P, Maamies T, Gröhn P: Emergency pericardiotomy as primary diagnostic and therapeutic procedure in malignant pericardial tamponade: Report of three cases and review of the literature. *J Surg Oncol* 1982; 21:18-22
20. Chen KTK: Extracardiac malignancy presenting with cardiac tamponade. *J Surg Oncol* 1983; 23:167-168
21. Lopez JM, Delgado JL, Tovar E, et al: Massive pericardial effusion procedure by extracardiac malignant neoplasms. *J Surg Oncol* 1983; 143:1815-1816
22. Fraser RS, Viloria JB, Wang N: Cardiac tamponade as a presentation of extracardiac malignancy. *Cancer* 1980; 45:1697-1704
23. Almagro UA, Carja JG, Remeniuk E: Cardiac tamponade due to malignant pericardial effusion in breast cancer: A case report. *Cancer* 1982; 49:1929-1933
24. Piehler JM, Pluth JR, Schaff HV, et al: Surgical management of effusive pericardial disease. *J Thorac Cardiovasc Surg* 1985; 90:506-516
25. Davis S, Rambotti P, Grighani F: Intrapericardial tetracycline sclerosis in the treatment of malignant pericardial effusion: An analysis of thirty-three cases. *J Clin Oncol* 1984; 2:631-636
26. Buck M, Ingle JN, Giuliani ER, et al: Pericardial effusion in women with breast cancer. *Cancer* 1987; 60:263-269

27. Posner MR, Cohen GI, Skarin AT: Pericardial disease in patients with cancer—The differentiation of malignant from idiopathic and radiation-induced pericarditis. *Am J Med* 1981; 71:407-413
28. Hancock EW: Pericardial disease—Differential diagnosis and management. *Hosp Pract* 1983; 18:101-112
29. Mill WB, Baglan RJ, Kurichety P, et al: Symptomatic radiation-induced pericarditis in Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1984; 10:2061-2065
30. Martin RG, Ruckdeschel JC, Chang P, et al: Radiation-related pericarditis. *Am J Cardiol* 1975; 35:216-220
31. Kagan AR, Hafermann M, Hamilton M, et al: Etiology, diagnosis and management of pericardial effusion after irradiation. *Radiol Clin Biol* 1971; 41:171-182
32. Applefeld MM, Cole JF, Pollock SH, et al: The late appearance of chronic pericardial disease in patients treated by radiotherapy for Hodgkin's disease. *Ann Intern Med* 1981; 94:338-341
33. Ruckdeschel JC, Chang P, Martin RG, et al: Radiation-related pericardial effusions in patients with Hodgkin's disease. *Medicine (Baltimore)* 1975; 54:245-259
34. Krikorian JG, Hancock EW: Pericardiocentesis. *Am J Med* 1978; 65:808-814
35. Ahmed M, Slayton RE: Report on drug-induced pericarditis (Letter). *Cancer Treat Rep* 1980; 64:353-355
36. Goldie RB: Secondary tumors of the heart and pericardium. *Br Heart J* 1955; 17:183-188
37. Agner RC, Gallis HA: Pericarditis—Differential diagnostic considerations. *Arch Intern Med* 1979; 139:407-412
38. Hurst JW, Cooper HR: Neoplastic disease of the heart. *Am Heart J* 1955; 50:782-802
39. Smith FE, Lane M, Hudgins PT: Conservative management of malignant pericardial effusion. *Cancer* 1974; 33:47-57
40. Reyes VC, Strinden C, Banerji M: The role of cytology in neoplastic cardiac tamponade. *Acta Cytol* 1982; 26:299-302
41. Yazdi HM, Hajdu SI, Melamed MR: Cytopathology of pericardial effusions. *Acta Cytol* 1980; 24:401-412
42. Zipf RE, Johnston WW: The role of cytology in the evaluation of pericardial effusions. *Chest* 1972; 62:593-596
43. Tatsuta M, Yamamura H, Yamamoto R, et al: Carcinoembryonic antigens in the pericardial fluid of patients with malignant pericarditis. *Oncology* 1984; 41:328-330
44. Sobol SM, Thomas HM Jr, Evans RW: Myocardial laceration not demonstrated by continuous electrocardiographic monitoring occurring during pericardiocentesis. *N Engl J Med* 1975; 292:1222-1223
45. Wong B, Murphy J, Chang CJ, et al: The risk of pericardiocentesis. *Am J Cardiol* 1979; 44:1110-1114
46. Morin JE, Hollomby D, Gonda A, et al: Management of uremic pericarditis: A report of 11 patients with cardiac tamponade and a review of the literature. *Ann Thorac Surg* 1976; 22:588-592
47. Guberman BA, Fowler NO, Engel PJ, et al: Cardiac tamponade in medical patients. *Circulation* 1981; 64:633-640
48. Callahan JA, Seward JB, Tajik AJ, et al: Pericardiocentesis assisted by two-dimensional echocardiography. *J Thorac Cardiovasc Surg* 1983; 85:877-879
49. Callahan JA, Seward JB, Nishimura RA, et al: Two-dimensional echocardiographically guided pericardiocentesis: Experience in 117 consecutive patients. *Am J Cardiol* 1985; 55:476-479
50. Clarke DP, Cosgrove DO: Real-time ultrasound scanning in the planning and guidance of pericardiocentesis. *Clin Radiol* 1987; 38:119-122
51. Johnson MH, Soulen RI: Echocardiography of cardiac metastases. *AJR* 1983; 141:677-681
52. Chandraratna PAN, Aronow WS: Detection of pericardial metastasis by cross-sectional echocardiography. *Circulation* 1981; 63:197-199
53. Grenadier E, Lima CO, Barron JV, et al: Two-dimensional echocardiography for evaluation of metastatic cardiac tumors in pediatric patients. *Am Heart J* 1984; 107:122-126
54. Tominaga K, Shinkai T, Eguchi K, et al: The value of two-dimensional echocardiography in detecting malignant tumors in the heart. *Cancer* 1986; 58:1641-1647
55. Hirsch DM Jr, Nydick I, Farrow JH: Malignant pericardial effusion secondary to metastatic breast carcinoma—A case of long-term remission. *Cancer* 1966; 19:1269-1272
56. Flannery EP, Gregoratos G, Corder MP: Pericardial effusions in patients with malignant diseases. *Arch Intern Med* 1975; 135:976-977
57. Hausheer FH, Yarbro JW: Diagnosis and treatment of malignant pleural effusion. *Semin Oncol* 1985; 12:54-75
58. Davis S, Sharma SM, Blumberg ED, et al: Intrapericardial tetracycline for the management of cardiac tamponade secondary to malignant pericardial effusion. *N Engl J Med* 1978; 299:1113-1114
59. Shepherd FA, Ginsberg JS, Evans WK, et al: Tetracycline sclerosis in the management of malignant pericardial effusion. *J Clin Oncol* 1985; 3:1678-1682
60. Shepherd FA, Morgan CD, Evans WK, et al: Medical management of malignant pericardial effusion by tetracycline sclerosis. *Am J Cardiol* 1987; 60:1161-1166
61. Thorsrud GK: Pleural reactions to irritants—An experimental study with special reference to pleural adhesions and concrescence in relation to pleural turnover of fluid. *Acta Chir Scand* 1965; 355(suppl):1-108
62. Sahn S, Good JT Jr: Experimental pleural symphysis: Results of differing sclerosing agents (Abstr). *Clin Res* 1980; 28:83A
63. Weisberger AS, Levine B, Storaasli JP: Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. *JAMA* 1955; 159:1704-1707
64. Goldman BS, Pearson FG: Malignant pericardial effusion. *Can J Surg* 1965; 8:157-161
65. Suhland LG, Weisberger AS: Intracavitary 5-fluorouracil in malignant effusions. *Arch Intern Med* 1965; 116:431-433
66. Cohen JL: Neoplastic pericarditis. *Cardiovasc Clin* 1976; 7:257-269
67. Maher E, Buckman R: Intrapericardial instillation of bleomycin in malignant pericardial effusion. *Am Heart J* 1986; 111:613-614
68. Wei JY, Taylor GJ, Achuff SC: Recurrent cardiac tamponade and large pericardial effusions: Management with an indwelling pericardial catheter. *Am J Cardiol* 1978; 42:281-282
69. Mufti GJ, Osier DG, Hamblin TJ, et al: Serous effusion in monocytic leukemias. *Br J Haematol* 1984; 58:547-552
70. Aymard JP, Voiriot P, Witz F, et al: Péricardite inaugurale d'une leucémie aiguë monoblastique—Description d'un cas et revue de la littérature. *Ann Med Interne (Paris)* 1980; 131:302-304
71. Peterson CD, Robinson WA, Kurnick JE: Involvement of the heart and pericardium in malignant lymphomas. *Am J Med Sci* 1976; 272:161-165
72. Primrose WR, Clee MD, Johnston RN: Malignant pericardial effusion managed with vinblastine. *Clin Oncol* 1983; 9:67-70
73. Reynolds PM, Byrne MJ: The treatment of malignant pericardial effusion in carcinoma of the breast. *Aust NZ J Med* 1977; 7:169-171
74. Terry LN, Kligerman M: Pericardial and myocardial involvement by lymphomas and leukemias—The role of radiotherapy. *Cancer* 1970; 25:1003-1008
75. Cham WC, Freiman AH, Carstens PHB, et al: Radiation therapy of cardiac and pericardial metastases. *Radiology* 1975; 114:701-704
76. Kaetz HW, Selsky LM: X-ray therapy in the treatment of cardiac tamponade in chronic myelocytic leukemia—Report of a case. *Conn Med* 1968; 32:523-524
77. Liedtke AJ, Adams DF, Weber ET, et al: Remission of cardiac lymphoma with super voltage radiation. *Am J Med* 1971; 50:816-822
78. Martini N, Freiman AH, Watson RC, et al: Intrapericardial instillation of radioactive chromic phosphate in malignant pericardial effusion. *AJR* 1977; 128:639-641
79. McKenna RJ, Ali MK, Ewer MS, et al: Pericardial effusions. *Curr Probl Cancer* 1985; 9:24-44
80. Miller JJ, Mansour KA, Hatcher CR Jr: Pericardiectomy: Current indications, concepts, and results in a university center. *Ann Thorac Surg* 1982; 34:40-45
81. Gregory JR, McMurtrey MJ, Mountain CF: A surgical approach to the treatment of pericardial effusion in cancer patients. *Am J Clin Oncol* 1985; 8:319-323
82. Ghosh SC, Larrieu AJ, Ablaza SGG, et al: Clinical experience with subxyphoid pericardial decompression. *Int Surg* 1985; 70:5-7
83. Hankins JR, Satterfield JR, Aisner J, et al: Pericardial window for malignant pericardial effusion. *Ann Thorac Surg* 1980; 30:465-471
84. Osuch JR, Khandekar JD, Fry WA: Emergency subxyphoid pericardial decompression for malignant pericardial effusion. *Am Surg* 1985; 51:298-300
85. Little AG, Kremser PC, Wade JL, et al: Operation for diagnosis and treatment of pericardial effusions. *Surgery* 1984; 96:738-744
86. Prager RL, Wilson GH, Bender HW: The subxyphoid approach to pericardial disease. *Ann Thorac Surg* 1982; 34:6-9
87. Alcan KE, Zabetakis PM, Marino ND, et al: Management of acute cardiac tamponade by subxyphoid pericardiotomy. *JAMA* 1982; 247:1143-1148
88. Hill GJ, Cohen BI: Pleural pericardial window for palliation of cardiac tamponade due to cancer. *Cancer* 1970; 26:81-93
89. Berman K, Fielding LP, Richi AA: Diagnosis and treatment of malignant pericardial effusion: The subxyphoid approach. *Conn Med* 1984; 48:701-702
90. Liepman MK, Goodlerner S: Surgical management of pericardial tamponade as a presenting manifestation of acute leukemia. *J Surg Oncol* 1981; 17:183-188
91. Press OW, Livingston R: Management of malignant pericardial effusion and tamponade. *JAMA* 1987; 257:1088-1092